REG-14863378

VAUZGE

NLM -- W1 CL731U (Gen): E-Journal w/ILL access

US PATENT AND TRADEMARK OFFICE
SCIENTIFIC AND TECHNICAL INFO CTR
107 S. WEST STREET, PMB 803
ALEXANDRIA, VA 22314

ATTN:
PHONE: 571-272-2517
FAX: 571-272-0230
E-MAIL: STIC-DOCS@uspto.gov

SUBMITTED: 2010-01-15 07:10:28
PRINTED: 2010-01-15 10:23:50
REQUEST NO.: REG-14863378
SENT VIA: DOCLINE
DOCLINE NO.: 28433694
OPAC NO.: SSSOSSS

REG Copy Journal

TITLE: CLINICAL NEUROPHARMACOLOGY
PUBLISHER/PLACE: Lippincott Williams & Wilkins Hagerstown, MD :
VOLUME/ISSUE/PAGES: 1995 Apr;18(2):95-112 95-112
DATE: 1995
AUTHOR OF ARTICLE: Slavoski LA;Tunkel AR
TITLE OF ARTICLE: THERAPY OF FUNGAL MENINGITIS.
ISSN: 0362-5664
OTHER NUMBERS/LETTERS: Unique ID.: 7607910
28433694
8635178
SOURCE: PubMed
MAX COST: $4.00
COPYRIGHT COMP.: Guidelines
CALL NUMBER: W1 CL731U (Gen); E-Journal w/ILL access

REQUESTER INFO: 700726
DELIVERY: E-mail Post to Web: STIC-DOCS@uspto.gov
REPLY: Mail:

KEEP THIS RECEIPT TO RECONCILE WITH BILLING STATEMENT
For problems or questions, contact NLM at http://wwwcf.nlm.nih.gov/ill/ill_web_form.cfm or phone 301-496-5511.
Include LIBID and request number.

Clinical Neuropharmacology
Vol. 18, No. 2, pp. 95–112

Review

Therapy of Fungal Meningitis

Linda A. Slavoski and Allan R. Tunkel

Division of Infectious Diseases, Medical College of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.

Summary: There has been an increase in recent years in the number of reported cases of meningitis and brain abscesses caused by fungi. This increase is due to the availability of better diagnostic techniques for fungal infections and the ever-increasing population of immunocompromised hosts (1,2). The patients most susceptible to invasive fungal infections include those with hematologic malignancies; those receiving hyperalimentation, corticosteroids, or cytotoxic drugs; transplant recipients; injection drug abusers; and those with the acquired immunodeficiency syndrome (AIDS). Although many fungi infect only immunologically impaired patients, some will infect normal hosts as well. The successful treatment of central nervous system (CNS) fungal infections is highly dependent on the underlying immune status of the host, as well as on the prompt initiation of appropriate antifungal therapy. However, the diagnosis of these infections may be difficult, and proper therapy often delayed. Furthermore, information on treatment regimens ranges from extensive, as in the case of cryptococcal meningitis, to scanty or nonexistent in the case of rare, opportunistic fungi. For >3 decades, the standard antifungal agent for the treatment of CNS fungal infections has been amphotericin B. However, the effectiveness of amphotericin B is often limited by poor CNS penetration, fungal resistance, and toxicity (3). Because of the problems associated with use of amphotericin B, newer azole antifungal agents have been developed, some of which are efficacious in the therapy of fungal meningitis. We give an overview of the antifungal agents currently available for clinical use and their utility in the treatment of fungal meningitis. Key Words: Antifungal—Amphotericin B—Meningitis.

ANTIFUNGAL AGENTS

Amphotericin B

Amphotericin B, the first commercially significant antifungal agent, has been available for >30 years. It is a by-product of the fermentation process of *Streptomyces nodosus*, first isolated at Squibb Laboratories in 1953 (4). Amphotericin B is a member of the polyene macrolide class of antibiotics and acts, at least in part, by binding irreversibly to ergosterol, a sterol present in the membrane of

Address correspondence and reprint requests to Dr. A. R. Tunkel, Division of Infectious Diseases, Medical College of Pennsylvania, 3300 Henry Avenue, Philadelphia, PA 19129, U.S.A.

sensitive fungi (3). This alters fungal membrane permeability, causing leakage of cell components and subsequent cell death. Other proposed mechanisms of action include oxidative damage and immunomodulation (5).

The pharmacokinetic properties of amphotericin B are summarized in Table 1 (6). After intravenous administration, amphotericin B becomes ~95% protein bound, primarily to lipoproteins, erythrocytes, and cholesterol. Cerebrospinal fluid (CSF) concentrations are thought to be only ~2–4% of simultaneous serum concentrations after intravenous administration (3). However, animal model data suggest that meningeal concentrations may be higher than CSF concentrations (7), which may account for the success of amphotericin B in the therapy of fungal meningitis. The metabolism of amphotericin B is poorly understood. Only a small percentage (3%) is excreted in the urine or bile. Serum concentrations are not influenced by the presence of hepatic or renal failure (8); hemodialysis does not generally reduce serum concentrations (9). Amphotericin B is usually administered by slow intravenous infusion over 2–6 h.

Unfortunately, amphotericin B is not without toxicity or adverse reactions. An acute reaction, usually in the form of rigors, may begin ~30–90 min after the start of the infusion, sometimes accompanied by hypoxemia, hypotension, or hypertension. Meperidine, given intravenously, has been shown to ameliorate the duration or severity of the rigors. In addition, intravenous hydrocortisone (25–50 mg) given before the amphotericin B infusion, or in the infusion, often diminishes the febrile reaction.

Renal failure is the most significant potential toxic effect of amphotericin B administration. Reversible impairment of renal function occurs early during the treatment and may occur in >80% of patients receiving therapy (3); return to pretreatment values may take up to several months. A therapeutic course of amphotericin B is usually followed by a permanent reduction in glomerular filtration rate, which appears to be unrelated to azotemia during therapy, but correlates with total dose (5). There is also a reduction in renal blood flow and impaired proximal and distal tubular reabsorption of electrolytes. The clinical manifestations include renal tubular acidosis, azotemia, oliguria, hypokalemia, and hypomagnesemia. Renal function does not deteriorate more often in renal transplant patients, diabetic patients, or those with preexisting renal impairment (10). Other effects of amphotericin B include thrombophlebitis and a normochromic, normocytic anemia; rarely, leukopenia, headache, anorexia, nausea, vomiting, myalgias, and arthalgias may occur. Intrathecal administration of amphotericin B may

TABLE 1. *Selected pharmacologic properties of systemic antifungal agents*[a]

Property	Amphotericin B	Flucytosine	Ketoconazole	Itraconazole	Fluconazole
Oral bioavailability (%)	<5	>80	75	>70	>80
Protein binding (%)	91–95	4	99	>99	11
Terminal elimination half-life	15 days	3–6 h	7–10 h[b]	24–42 h[b]	22–31 h
Cerebrospinal fluid penetration (%)	2–4	>75	<10	<1	>70

[a] Adapted from reference 6.
[b] Longer terminal elimination half-lives are possible with large daily doses.

rmeability, causing leakage of
roposed mechanisms of action
(5).
B are summarized in Table 1
in B becomes ~95% protein
id cholesterol. Cerebrospinal
~2–4% of simultaneous serum
However, animal model data
r than CSF concentrations (7),
in B in the therapy of fungal
orly understood. Only a small
Serum concentrations are not
ire (8); hemodialysis does not
otericin B is usually adminis-

icity or adverse reactions. An
gin ~30–90 min after the start
emia, hypotension, or hyper-
shown to ameliorate the du-
enous hydrocortisone (25–50
the infusion, often diminishes

oxic effect of amphotericin B
ction occurs early during the
eiving therapy (3); return to
ths. A therapeutic course of
reduction in glomerular filtra-
during therapy, but correlates
nal blood flow and impaired
lytes. The clinical manifesta-
aria, hypokalemia, and hypo-
nore often in renal transplant
renal impairment (10). Other
and a normochromic, normo-
xia, nausea, vomiting, myal-
ration of amphotericin B may

ystemic antifungal agents[a]

nazole	Itraconazole	Fluconazole
5	>70	>80
9	>99	11
) h[b]	24–42 h[b]	22–31 h
0	<1	>70

ses.

be required for therapy of certain causes of fungal meningitis (see the following) and has been associated with headache, delirium, arachnoiditis, vasculitis, radiculopathy, myelopathy, visual impairment, and meningitis (chemical or bacterial) (2).

Flucytosine

Flucytosine is the fluorine analog of the body constituent cytosine and is readily absorbed intact from the gastrointestinal tract. Its mechanism of action depends on the enzyme cytosine deaminase, which is found in susceptible fungi and converts flucytosine to the antimetabolite 5-fluorouracil, with subsequent conversion to 5-fluorodeoxyuridine monophosphate, a noncompetitive inhibitor of thymidylate synthetase (11). This interferes with fungal DNA synthesis.

The pharmacokinetic properties of flucytosine are summarized in Table 1 (6). Flucytosine is completely absorbed after oral administration, and there is negligible protein binding. Approximately 90% of the drug is excreted unchanged in the urine. CSF concentrations average 74% of simultaneous serum concentrations. The half-life of flucytosine in patients with normal renal function is 3–6 h; decreased renal function prolongs the half-life.

Flucytosine is usually administered as 150 mg/kg/day in four divided doses in patients with a creatinine clearance >50 ml/min. The total dose should be reduced to 75 mg/kg/day in patients with a creatinine clearance of 26–50 ml/min, and 37 mg/kg/day when the creatinine clearance is reduced to 13–25 ml/min. Patients receiving hemodialysis may be given a single dose of 37 mg/kg after each dialysis (12). Despite the adjustment in doses, serum concentrations must be followed and should be maintained at 50–100 μg/ml. Complications appear to be more frequent when flucytosine serum concentrations exceed 100–125 μg/ml and include thrombocytopenia, leukopenia, hepatic dysfunction, diarrhea, anorexia, nausea, and vomiting (12,13). Serum concentrations must be obtained (2 h after a dose) and dosing adjusted accordingly. It is recommended that the serum creatinine be monitored twice weekly, and the creatinine clearance calculated weekly during therapy to anticipate changes in serum flucytosine concentrations.

Flucytosine should never be given alone for the treatment of CNS infections because fungi have developed in vitro and in vivo resistance during single-drug therapy. Therefore, clinicians have generally used this drug in combination with amphotericin B. The additive effects of the two drugs allow use of lower amphotericin B doses, thereby causing less amphotericin B–related toxicity (12). Flucytosine resistance during combination therapy is rare.

Azole Antifungal Agents

The azole class of antifungal agents can be divided into two groups: the imidazoles, which include miconazole and ketoconazole; and the triazoles, which include fluconazole and itraconazole (6,14,15). All of these compounds are synthetic and structurally similar, with a five-member azole ring and a complex side

chain attached to one of the nitrogen atoms. Imidazole antifungal agents contain two nitrogen atoms within the five-member ring, whereas the triazoles contain three nitrogen atoms.

The antifungal effects of the azoles are targeted primarily at ergosterol, the main sterol of the fungal cell membrane (6). The azoles inhibit ergosterol synthesis through an interaction with C-14 α-demethylase, an enzyme dependent on cytochrome P-450, which is necessary for the conversion of lanosterol to ergosterol. The depletion of ergosterol alters membrane fluidity, as well as membrane permeability.

In general, the azole drugs have been well tolerated. Dose-related gastrointestinal symptoms are the most common side effects but rarely necessitate the discontinuation of therapy (6,14). Other adverse effects include headache, fever, fatigue, abdominal pain, and diarrhea; hypersensitivity reactions rarely occur. There is the potential for hepatic toxicity, which is seen more often with ketoconazole than with the other azole antifungal agents. Drug–drug interactions are another major concern and may be seen in patients receiving H_2-receptor antagonists, phenytoin, rifampin, cyclosporine, sulfonylurea drugs, terfenadine, astemizole, or warfarin (16). The azoles receiving the most clinical attention are ketoconazole, fluconazole, and itraconazole; these are discussed in more detail subsequently.

Ketoconazole

Ketoconazole is available only for oral administration. It is a weak base that requires an acid environment for optimal oral absorption (6). Concomitant use of H_2-blocking agents, gastric surgery, or gastropathy associated with AIDS may reduce gastric acid secretion and therefore decrease absorption. Ketoconazole is extensively bound to plasma proteins, thus limiting the distribution of the drug. Penetration into the CSF is poor (Table 1); failure of ketoconazole treatment for fungal meningitis has occurred. Ketoconazole is metabolized in the liver, so dosage need not be adjusted for renal failure.

Side effects after therapy with ketoconazole include nausea, vomiting, hepatotoxicity, and endocrinologic toxicity (6). Transient elevations in serum transaminases and alkaline phosphatase may occur but usually return to normal during treatment. Clinical hepatitis has been reported; hepatotoxicity is usually reversible when the drug is discontinued, however. The main difference in potential toxicity between ketoconazole and the newer azoles is its effect on steroidogenesis. Ketoconazole can reversibly inhibit the synthesis of adrenal and gonadal steroid hormones by inhibiting the cytochrome P-450 enzymes necessary for their synthesis, resulting in disturbances such as gynecomastia, oligospermia, impotence, menstrual irregularities, and occasionally, adrenal insufficiency.

Fluconazole

Fluconazole is available in both oral and intravenous formulations. The absorption of oral fluconazole is not altered by the presence of food or by gastric acidity,

and peak plasma concentrations are reached within 1 to 2 h after administration (6,17). In contrast to the other azole antifungals that are highly bound, plasma protein binding of fluconazole is low (~11%). Therefore, concentrations of fluconazole in most body tissues and fluids exceed 50% of the corresponding plasma concentrations. The primary route of elimination is renal, with ~80% of the administered dose being excreted in the urine. The dose should be reduced in patients with glomerular filtration rates <50 ml/min. Hemodialysis for 3 h generally reduces the serum concentration by 50%; the drug is also removed by peritoneal dialysis (14). The mean half-life ranges from 21 to 31 h (Table 1). The distinguishing feature of fluconazole that separates it from other azoles is its good penetration into CSF. Peak CSF concentrations of fluconazole are 70–90% of simultaneous peak plasma concentrations (18). The good absorption after oral dosing, long half-life, high volume of distribution, low level of protein binding, and high degree of penetration into CSF make fluconazole a potentially good agent for the treatment of fungal meningitis (19).

Side effects of fluconazole have been less than those noted with ketoconazole and include nausea, vomiting, rash, and asymptomatic elevations of serum transaminases; hepatitis is rare.

Itraconazole

Itraconazole is available only for oral administration and, like ketoconazole, is a weak base requiring an acid environment for optimal oral absorption (6,20). The bioavailability of itraconazole is two to three times higher when taken with food. Once absorbed, itraconazole becomes highly bound to plasma proteins and is extensively metabolized in the liver, although its half-life at steady-state conditions is 24–42 h. Because little drug is excreted in the urine, the dosage need not be adjusted for patients with renal impairment or those receiving dialysis. Itraconazole has relatively poor penetration into CSF (Table 1), but successful treatment of certain CNS fungal infections suggests that penetration of itraconazole into the meninges is more important than actual CSF penetration (see the following).

Side effects reported with itraconazole are mainly gastrointestinal and include nausea, vomiting, abdominal pain, headache, and dizziness (6,20). Hypokalemia, elevated serum transaminases, elevated alkaline phosphatase, pedal edema, and hypertension have also been reported. Itraconazole is contraindicated in pregnancy, except for therapy of life-threatening fungal infections. The drug–drug interactions with itraconazole are similar to those seen with ketoconazole.

FUNGAL PATHOGENS

The successful treatment of CNS fungal infections is highly dependent on the underlying immune status of the host. Therapy, in most cases, is more likely to be successful in patients who are only temporarily immunosuppressed, as compared to patients with persistence of their underlying immune deficits. Therapy is also more likely to be successful if begun early in the course of infection. However, the

diagnosis of these infections is often difficult, causing delay in the initiation of proper therapy, sometimes late in the disease course.

The clinical presentation of fungal meningitis is less stereotyped than that of bacterial meningitis, with patients most often first seen with the chronic meningitis syndrome (21). Numerous fungal species have been reported to cause meningitis (Table 2). Clinical manifestations, methods for diagnosis, and treatment recommendations (Table 3) are discussed separately for the more common fungi that cause meningitis.

Cryptococcus neoformans

C. neoformans is an encapsulated yeast-like fungus and is the only encapsulated yeast known to be pathogenic for humans. The cell is round or oval, usually 4–6 μm in diameter (22). It reproduces by budding. *C. neoformans* is ubiquitous in nature and has been isolated from soil, pigeon excrement, and sites contaminated by pigeon or other avian excrement. Nonavian sources include fruits, vegetables, and dairy products (23,24).

Before the advent of the AIDS epidemic, cryptococcal meningitis was rare. Now *C. neoformans* is the most common fungal cause of clinically recognized meningitis; patients with AIDS constitute the highest risk group for cryptococcal meningitis (25–28). Whereas *Cryptococcus* is greatly increased in frequency in patients with defective cell-mediated immunity, before the AIDS epidemic, ~50% of all patients with cryptococcal infection had no readily identifiable underlying immune defect. Those who are also at risk include patients with a lymphoreticular malignancy (e.g., lymphoma), diabetes mellitis, chronic renal failure, collagen vascular diseases (e.g., systemic lupus erythematosus), and patients receiving organ transplants or immunosuppressive agents (29–31). Cryptococcal infection has been described in all age groups, but two thirds of patients are between the ages of 30 and 50 years (2).

The respiratory route is the usual means of primary infection, which can be followed by disseminated disease (32). Meningitis is the most common form of CNS disease caused by *C. neoformans*, but the organism may also cause brain abscesses and granulomas, either alone or in association with meningitis.

TABLE 2. *Fungal pathogens that may cause meningitis*

Aspergillus species
Blastomyces dermatitidis
Candida species
Cladosporium species
Coccidioides immitis
Cryptococcus neoformans
Dematiacious fungi
Histoplasma capsulatum
Paracoccidioides brasiliensis
Pseudallescheria boydii
Sporothrix schenckii
Zygomycetes species

TABLE 3. *Specific antifungal therapy for meningitis*

Fungus	Standard therapy	Alternative therapies
Cryptococcus neoformans	Amphotericin B ± flucytosine[a]	Fluconazole, itraconazole[b]
Coccidioides immitis	Amphotericin B[c]	Fluconazole, itraconazole[b]
Candida species	Amphotericin B ± flucytosine[a]	Fluconazole[b]
Histoplasma capsulatum	Amphotericin B	Itraconazole[b], fluconazole[b]
Blastomyces dermatitidis	Amphotericin B	

[a] Monitor serum concentrations and maintain at 50–100 μg/ml.
[b] Effectiveness of this agent has not been established.
[c] Intravenous and intrathecal administration.

Cryptococcal meningitis occurs differently in non-AIDS patients and AIDS patients (24–30,33). In non-AIDS patients, headache, nausea, vomiting, meningeal signs, and mental-status changes are common as opposed to a nonspecific presentation with minimal findings in patients with AIDS; the only clinical findings may be headache, fever, and lethargy. Ocular abnormalities (seen in ~40% of patients) associated with raised intracranial pressure may occur and include papilledema, cranial nerve palsies, blind spots, and reduced visual acuity (34).

CSF findings in most non-AIDS patients show a pleocytosis, predominately lymphocytic, elevated protein concentration, and often reduced glucose (30,31). AIDS patients, on the other hand, may have low CSF white blood cell counts (65% of patients have <5 white blood cells/mm^3) and a normal glucose concentration (in two thirds of cases) (27,30,33). The CSF protein concentration is usually elevated. AIDS patients with completely normal CSF have been reported (35). The yield of CSF culture for isolation of *C. neoformans* is excellent in both non-AIDS and AIDS patients. India ink examination is a rapid, effective test, which is positive in 50–75% of patients with cryptococcal meningitis (this yield increases up to 88% in AIDS patients), but should always be confirmed with culture.

Several serologic tests for cryptococcal disease exist, but the most useful is the latex agglutination test for the detection of cryptococcal polysaccharide antigen (36,37). A presumptive diagnosis of cryptococcal meningitis is indicated by a CSF titer ≥1:8. Serum cryptococcal polysaccharide antigen may also be detected, particularly in severely immunocompromised patients (i.e., those with AIDS) (27), although the value of the serum cryptococcal polysaccharide antigen to screen patients suspected of having meningeal disease has not been established. In normal hosts with cryptococcal meningitis, serum titers are usually negative or are lower than CSF titers. False-negative tests are unusual but may be negative in early infection when the CSF burden of *Cryptococcus* is low or secondary to a prozone phenomenon from antigen excess. A small number of false positives do occur, usually in the presence of rheumatoid factor, malignancy, or collagen vascular disease. The overall sensitivity and specificity of the cryptococcal polysaccharide antigen test are close to 100% (38).

Prognosis of cryptococcal infection depends on the underlying predisposing condition as well as the severity of disease at the time of diagnosis. In non–HIV-

infected individuals, prognostic factors have been clearly delineated. Poor prognostic indicators include an initial positive CSF India ink test, an elevated opening pressure, an initial CSF white blood cell count of $<20/mm^3$, culture of *C. neoformans* from any extraneural site, an initial cryptococcal antigen titer $\geq$1:32 in CSF, and the coexistence of corticosteroid use or hematologic malignancy (21, 28,29). Patients were more likely to relapse after treatment if they had one or more of the following: a CSF glucose concentration that remained abnormal during 4 or more weeks of therapy, low initial CSF white blood cell counts ($<20/mm^3$), cryptococci isolated from extraneural sites, absent anticryptococcal antibody, post-treatment CSF or serum titer $\geq$1:8, no significant decrease in CSF or serum antigen titers during therapy, or daily corticosteroid therapy (equivalent to 20 mg of prednisone or more) after completion of therapy (29). In HIV-infected patients, poor prognostic signs include high antigen titers in CSF (>1:10,000), altered mental status, and abnormal computed tomography (CT) of the head (26).

Before the clinical availability of amphotericin B, cryptococcal meningitis was nearly always fatal. With its introduction, prognosis improved, although relapse rates remained high, especially in immunocompromised patients (cure rates $\leq$52% after the first course of therapy) (30). Once it was demonstrated that amphotericin B had in vitro synergistic activity with flucytosine, trials with amphotericin B in combination with flucytosine compared to amphotericin B alone were done. A large prospective collaborative trial compared combination therapy with amphotericin B (0.3 mg/kg/day) plus flucytosine (150 mg/kg/day) for 6 weeks to amphotericin B (0.4 mg/kg/day) alone for 10 weeks in patients with cryptococcal meningitis (39). Combination therapy produced fewer failures, fewer relapses, more rapid sterilization of CSF, and decreased nephrotoxicity; cure or improvement occurred in 67% of patients receiving combination therapy versus 41% of patients receiving amphotericin B alone. Mortality rates in the two groups were not statistically different. However, this trial has been criticized because of the low dose of amphotericin B used in the single-agent arm of the study.

A subsequent study of the therapy of cryptococcal meningitis compared a 4-week to a 6-week regimen of amphotericin B plus flucytosine (40). The study demonstrated that a 4-week regimen could be used in the subset of patients who at presentation had no neurologic complications, no underlying diseases, no immunosuppressive therapy, a pretreatment CSF white blood cell count $>20/mm^3$, and a serum cryptococcal polysaccharide antigen titer $<$1:32; and at 4 weeks had a negative CSF India ink and a CSF cryptococcal polysaccharide antigen titer $<$1:8. However, patients treated with combination therapy were noted to have a high rate of toxicity related to therapy with flucytosine (38% of cases) (10), mainly hematologic, indicating the need to monitor serum concentrations (see previous sections).

In AIDS patients with cryptococcal meningitis, therapy initially consisted of standard antifungal therapy. In a retrospective analysis of AIDS patients with cryptoccocal meningitis (27), no differences in survival were noted whether patients were treated with amphotericin B alone or amphotericin B plus flucytosine. However, in >50% of the patients receiving flucytosine, therapy had to be discontinued because of toxicity, primarily cytopenias.

Because of poor response to amphotericin B therapy in AIDS patients with cryptococcal meningitis, there is a search for alternative therapeutic options, primarily with the azole antifungal agents. Fluconazole, with its long half-life and excellent CSF penetration, appeared to be a very promising agent, although initial enthusiasm was based on small, uncontrolled studies (41,42). However, two recent studies in AIDS patients compared fluconazole therapy to standard antifungal therapy. In the first trial, fluconazole (400 mg/day) was compared to amphotericin B (0.7 mg/kg/day) plus flucytosine (150 mg/kg/day) (43). Eight of the 14 patients receiving fluconazole failed therapy versus none of the six patients receiving amphotericin B plus flucytosine; combination therapy had superior clinical and mycologic efficacy. A second study compared fluconazole (400-mg initial dose followed by 200 mg/day) to amphotericin B alone (at least 0.3 mg/kg/day) for cryptococcal meningitis in AIDS patients (44). No significant differences were found in the number of patients who were cured or improved or in overall case fatality rates, but there was a trend to early mortality (within the first 2 weeks) in patients treated with fluconazole. In addition, in a post hoc analysis of the data, it appeared that fluconazole was an effective alternative to amphotericin B as primary treatment in AIDS patience with cryptococcal meningitis who were without certain negative prognostic signs such as a positive blood culture for *C. neoformans*, CSF cryptococcal polysaccharide antigen titer >1:128, positive India ink smear, or altered mentation (45). However, this study has been criticized because the drug dosages used in both arms of the study may have been too low for optimal therapy of cryptococcal meningitis. Although the optimal therapy of cryptococcal meningitis in AIDS patients is unknown, these data support the initial use of amphotericin B, with or without flucytosine, for a period of ~2 weeks; this period may need to be prolonged in patients who are severely ill. Patients should then receive fluconazole (400 mg/day) to complete a 10-week course. Pending further data, non-AIDS patients with cryptococcal meningitis should continue to receive standard therapy with amphotericin B plus flucytosine for 4–6 weeks (see previous sections).

Another concern in AIDS patients with cryptococcal meningitis is relapse after completion of therapy. An important reservoir for recurrent cryptococcal infection appears to be the prostate gland, even after effective therapy for meningitis (46,47). This supports the need for chronic suppressive therapy. Long-term suppressive therapy in AIDS patients using either ketoconazole or amphotericin B has been associated with improved survival (238 vs. 141 days) (27), although maintenance therapy with amphotericin B (50–100 mg/weekly) does not quarantee protection against relapse of cryptococcosis in patients with AIDS (48). Several studies have examined the utility of fluconazole for preventing relapse of cryptococcal meningitis in patients with AIDS (49). A placebo-controlled trial showed that the rate of relapse was markedly diminished in patients receiving suppressive therapy (3 vs. 37% in patients using placebo) (50). A subsequent trial compared fluconazole (200 mg/day) to amphotericin B (1 mg/kg/week) and revealed that fluconazole was superior (relapse rate of 2 vs. 18% in patients receiving amphotericin B) (51). These data indicate that fluconazole (200 mg/day) is the antifungal agent of choice to prevent relapse of cryptococcal meningitis in patients with

AIDS. Suppressive therapy must be continued for life. Maintenance therapy with itraconazole is being studied.

Coccidioides immitis

C. immitis is a dimorphic fungus that grows in soil in the mycelial phase (52). It is endemic to the semiarid regions and desert of the southwest portion of the United States (California, Arizona, New Mexico, Texas) and regions of Mexico, Central America, and South America (52–55). The areas of highest endemicity are the southern San Joaquin Valley of California and southern Arizona.

Infection results from inhalation of airborne *C. immitis* arthroconidia (56); person-to-person tranmission does not occur. The arthroconidia swell and form large-walled spherules that are 30–200 μm in diameter. The spherule produces up to 800 endospores that are ~2–5 μm in size and are released on rupture, forming new spherules. Dissemination outside the lungs occurs in ~0.5% of cases (53,57), usually within the first 6 months after initial infection. Of the patients who develop disseminated disease, one third to one half have meningeal involvement. Disseminated disease is associated with extremes of age, male gender, non-Caucasian race, pregnancy, and immunosuppression (1). Extrapulmonary coccidioidomycosis is an AIDS-defining illness when it occurs in a person with evidence of HIV infection.

When dissemination to the CNS occurs, meningitis usually is seen within 6 months after the primary infection and may occur acutely or almost coincident with primary infection (53,57). The main areas of involvement are the basilar meninges; space-occupying lesions are rare. The most common symptom is headache; personality changes, fever, weakness, confusion, seizures, diplopia, ataxia, and focal neurologic defects may also occur. Signs of meningeal irritation are usually absent, although they have been reported in up to one third of cases.

CSF from patients who have coccidioidomycosis reveals a pleocytosis in which mononuclear cells almost always predominate; a prominent eosinophilia is sometime seen (56,58). The glucose is decreased and protein concentration is elevated. Only 25–50% of patients have positive CSF cultures.

The most useful test available for diagnosis of coccidioidomycosis remains the complement-fixing antibody titer (CFA), which detects immunoglobulin G (IgG). Serum CFA titers >1:32–1:64 suggest disseminated disease (53,57); however, patients with coccidioidal meningitis may have low serum CFA titers when other body sites are not involved. Antibodies are present in at least 70% of patients with early disease and in virtually all patients with disease progression. In patients with meningitis, CFA titers are present in CSF and appear to parallel the course of meningeal disease. Therefore, they can be used as a basis for both diagnosis and treatment (57). The concentrated CSF will not fix complement in the absence of meningitis, eliminating the possibility of a false-positive complement-fixation result. Of note, complement-fixing antibodies may fail to develop in serum or CSF in patients who are immunodeficient.

The standard therapy of coccidioidal meningitis for the last 35 years has been amphotericin B, administered both intravenously and intrathecally (52,54,57), al-

though the optima
thecal administrati
an Ommaya reser
week for a total d
with hydrocortiso
multaneously to r
poorly tolerated,
apy is administer
nated foci; a syste
for duration of th
previously, is give
that the CSF is no
Close follow-up o
years. If a clinical
be retreated. Mort
(52,57), although o
75 months if large
(59). Patients are
without relapse.
underlying disease
the end of therapy

Because of the
antifungals are be
for the treatment
promising, most p
cin B. Recently, d
of coccidioidal me
coccidioidal menir
fluconazole (400 n
patients. Of the 47
within 4–8 months
patients exhibited
follow-up. The au
with intrathecal a
sponding patients,
currently under w
therapy of coccidi

Itraconazole has
(61). Despite lowe
400 mg daily have
most of the data
with amphotericin
tions can be made
indefinitely becau
tion of therapy. In
gal regimen has be

fe. Maintenance therapy with

l in the mycelial phase (52). It
the southwest portion of the
exas) and regions of Mexico,
reas of highest endemicity are
southern Arizona.
mitis arthroconidia (56); per-
oconidia swell and form large-
e spherule produces up to 800
sed on rupture, forming new
in ~0.5% of cases (53,57),
. Of the patients who develop
ningeal involvement. Dissem-
male gender, non-Caucasian
pulmonary coccidioidomyco-
person with evidence of HIV

gitis usually is seen within 6
acutely or almost coincident
involvement are the basilar
st common symptom is head-
on, seizures, diplopia, ataxia,
s of meningeal irritation are
1 up to one third of cases.
reveals a pleocytosis in which
ominent eosinophilia is some-
ein concentration is elevated.
s.
coccidioidomycosis remains the
cts immunoglobulin G (IgG).
ed disease (53,57); however,
serum CFA titers when other
n at least 70% of patients with
progression. In patients with
ear to parallel the course of
basis for both diagnosis and
omplement in the absence of
itive complement-fixation re-
to develop in serum or CSF

or the last 35 years has been
d intrathecally (52,54,57), al-

though the optimal intrathecal route and dose have not been determined. Intrathecal administration can occur via lumbar, cisternal, or ventricular (i.e., through an Ommaya reservoir) routes. The usual intrathecal dosage is 0.5 mg three times/week for a total dose of 20–25 mg; dosages of 1.0–1.5 mg can be used if combined with hydrocortisone. Intrathecal corticosteroids are commonly administered simultaneously to reduce local reactions. However, intrathecal amphotericin B is poorly tolerated, often leading to arachnoiditis. Intravenous amphotericin B therapy is administered, as a prophylactic treatment, against other occult disseminated foci; a systemic course of ~0.5–1.0 g is commonly given. Recommendations for duration of therapy vary. Once the initial intrathecal therapy, as outlined previously, is given, it is tapered to once every 6 weeks. When it is established that the CSF is normal for at least 1 year on this regimen, therapy is discontinued. Close follow-up of CSF is required approximately every 6 weeks for at least 2 years. If a clinical relapse or marked CSF abnormalities recur, the patient should be retreated. Mortality rates in coccidioidal meningitis of 50% have been reported (52,57), although one study documented a survival rate of 91% over a follow-up of 75 months if larger doses of intrathecal amphotericin B (1.0–1.5 mg) were used (59). Patients are considered cured only after they have survived for >5–8 years without relapse. An unfavorable outcome is associated with hydrocephalus, an underlying disease, and non-Caucasian race. Low or absent CFA titers in CSF at the end of therapy suggest a favorable outcome (57).

Because of the difficulty and toxicity associated with amphotericin B, the azole antifungals are being studied. Both fluconazole and itraconazole have been used for the treatment of coccidioidal meningitis. Although initial results appeared promising, most patients were treated previously or concurrently with amphotericin B. Recently, data have accumulated on the use of fluconazole in the treatment of coccidioidal meningitis. In one study (60), 50 consecutive patients with active coccidioidal meningitis (including nine HIV-infected patients) were treated with fluconazole (400 mg daily) for up to 4 years (median, 37 months) in responding patients. Of the 47 evaluable patients, 37 responded to treatment, most improving within 4–8 months of drug initiation. Despite the absence of symptoms, 24% of patients exhibited a persistent CSF pleocytosis, indicating the need for careful follow-up. The authors suggested that nonresponding patients should be treated with intrathecal amphotericin B or with increasing doses of fluconazole. In responding patients, therapy may need to be continued indefinitely. A large study is currently under way, using higher doses of fluconazole (800 mg daily), in the therapy of coccidioidal meningitis.

Itraconazole has also shown promise in the treatment of coccidioidal meningitis (61). Despite lower CSF penetration than fluconazole, itraconazole doses of 300–400 mg daily have shown a positive effect. Given the small study groups and that most of the data available are from patients treated previously or concurrently with amphotericin B, further comparative trials are needed before recommendations can be made. However, it is likely that the azoles will need to be given indefinitely because preliminary data indicate that relapses do occur after cessation of therapy. In HIV-infected patients with coccidioidal meningitis, no antifungal regimen has been proven superior. For now, a reasonable approach would be

to treat initially with amphotericin B, followed by chronic suppressive therapy with an effective azole agent.

Candida Species

Candida organisms are ~4–6 μm, thin-walled, ovoid organisms that reproduce in the yeast form, whereas pseudohyphae or hyphae are frequently found in infected tissue (62). Tissue invasion usually occurs in patients with altered host defenses or immunodeficiencies such as those with hematologic malignancy, neutropenia, diabetes mellitus, and in those receiving corticosteroid therapy, broad-spectrum antimicrobials, or hyperalimentation (62,63). There are >150 species of *Candida*, but only 10 are regarded as important pathogens for humans. *C. albicans* is the species most commonly isolated in CNS disease.

The CNS is frequently involved in patients with disseminated candidiasis; many reviews have reported CNS involvement to be ~50%. *Candida* infects both parenchymal brain tissue and the meninges; parenchymal lesions are usually in the form of multiple cerebral microabscesses. *Candida* meningitis is uncommon, occurring in <15% of patients with CNS candidiasis (64–66). Candidal meningitis mimics bacterial meningitis with fever and signs of meningeal irritation; nuchal rigidity, headache, and photophobia are often found.

The meningeal form of disease is often easier to diagnose than the other forms of CNS candidiasis, which often require a high degree of clinical suspicion. The CSF findings in candidal meningitis include a pleocytosis (mean, 600 cells/mm^3) with polymorphonuclear leukocyte predominance (64,65). Smears and cultures are very often positive. Recovery of *Candida* from other sites, including sputum, bone marrow, and pleural or peritoneal fluid, would suggest dissemination and possible CNS involvement. Serologic testing of both serum and CSF yield variable results and are not reliable.

The treatment of choice for *Candida* meningitis is amphotericin B with or without the addition of flucytosine (64,65). Some investigators recommend combination therapy based on more rapid CSF sterilization and possible reduction of long-term neurologic sequelae in newborns (2,67), although there are no studies comparing the efficacy of single-agent versus combination therapy. Amphotericin B at doses of 0.6 mg/kg/day are generally used. Cure rates have ranged from 71 to 100% in neonates and from 67 to 89% in adults with *Candida* meningitis, although sequelae have been observed in a high percentage of survivors (in surviving neonates, as many as 56% had psychomotor retardation and 50% had hydrocephalus). Increased mortality in adults has been associated with a delay of diagnosis from onset of symptoms of >2 weeks, a CSF glucose concentration <35 mg/dl, development of intracranial hypertension, and the presence of focal neurologic deficits. The role of azole antifungal agents (e.g., fluconazole) in the therapy of *Candida* meningitis remains to be defined.

Histoplasma capsulatum

H. capsulatum is a typical dimorphic yeast, existing in a mycelial form at room temperature and as a yeast at 37°C. It has been isolated from soil of areas in which

it is endemic and
oval, ~2–5 μm in
cells by narrow b
Ohio, Mississippi,
Lake Champlain
Carolina and Virg
Histoplasmosis
those younger th
often than female
Most cases of hist
of patients develo
curs in >90% of H
has been estimate
tion (2), taking the
moma.
The most com
include headache,
deficits (cranial n
include paralysis,
mon (~10% of ca
The CSF in pat
blood cell count r
predominate (1,70
glucose concentra
the CSF. Cultures
CSF samples are
importance of obt
meningitis. Large
separate occasion
weeks may be re
treatment in patie
Detection of s
Histoplasma men
antibodies to *His*
have been used fo
are less specific,
of cases (21). A
detection of *Histo*
(70,72–74); antige
Serologic tests fo
misleading, becau
with disseminate
diseases (due to c
(70). Furthermore
from histoplasmo
patients with neu

it is endemic and is highly concentrated in bird and bat feces. The yeast cells are oval, ~2–5 μm in diameter, and have blastoconidia that are attached to the parent cells by narrow bases. *H. capsulatum* is endemic to river valleys, including the Ohio, Mississippi, and the St. Lawrence River valleys (68). It is also found in the Lake Champlain region, along the Appalachian Mountains, and in parts of North Carolina and Virginia.

Histoplasmosis may be acquired at any age, the highest incidence occurring in those younger than 3 years and older than 40 years, with males affected more often than females (68). Infection is established on inhalation of airborne spores. Most cases of histoplasmosis are limited to the lungs, although a small percentage of patients develop disseminated infection; dissemination of histoplasmosis occurs in >90% of HIV-infected patients (69). The incidence of CNS histoplasmosis has been estimated to be between 10 and 24% of all cases of disseminated infection (2), taking the form of meningitis, miliary granulomas, or a solitary histoplasmoma.

The most common clinical neurologic abnormalities of CNS histoplasmosis include headache, depressed level of consciousness, confusion, and cranial nerve deficits (cranial nerves III, VI, and VII) (1,70). Other focal neurologic deficits include paralysis, ataxia, clonus, and seizures. Meningismus is relatively uncommon (~10% of cases).

The CSF in patients with *Histoplasma* meningitis is usually clear with a white blood cell count not exceeding 300/mm^3; either neutrophils or lymphocytes may predominate (1,70). The CSF protein concentration is generally elevated, and the glucose concentration is decreased (71). Yeast cells are rarely seen on staining of the CSF. Cultures of CSF are infrequently positive. In many cases, when multiple CSF samples are submitted, a single culture will be positive, emphasizing the importance of obtaining multiple specimens to exclude a diagnosis of *Histoplasma* meningitis. Large volumes (>10 ml) of CSF should be cultured on at least three separate occasions to increase the yield for isolation of fungi. However, up to 4 weeks may be required to identify *H. capsulatum* in positive cultures, delaying treatment in patients with more severe disease.

Detection of specific antibodies in the CSF has been used for diagnosis of *Histoplasma* meningitis because CSF culture is rarely positive (1,70). Detection of antibodies to *Histoplasma* by both complement-fixation and radioimmunoassay have been used for diagnosis. Although these tests have excellent sensitivity, they are less specific, and cross-reactions with other fungal pathogens occur in ~50% of cases (21). A more recent development in the diagnostic approach has been detection of *Histoplasma* polysaccharide antigen (HPA) in blood, CSF, and urine (70,72–74); antigen was detected in body fluids of >90% of cases that were tested. Serologic tests for anti–*H. capsulatum* antibodies may also be helpful but can be misleading, because these serologic tests may be negative in 10–25% of patients with disseminated histoplasmosis or falsely positive in patients with other fungal diseases (due to cross-reactivity with antigens shared with other fungal organisms) (70). Furthermore, antibody titers remain elevated for several years after recovery from histoplasmosis and may thus lead to a misdiagnosis of histoplasmosis in patients with neurologic illnesses caused by other diseases.

Treatment of disseminated histoplasmosis, including meningitis, has generally been with intravenous administration of amphotericin B in doses up to 0.7–1.0 mg/kg/day for a total dose of at least 30–35 mg/kg (1,21,70). Intrathecal or intraventricular administration has not been proven to be more efficacious. Fewer than 50% of patients with CNS histoplasmosis appear to be cured by antifungal therapy, compared to cure rates of 90% in patients with disseminated histoplasmosis not complicated by neurologic involvement.

With the AIDS epidemic, more experience has been gained in treating patients with disseminated histoplasmosis and CNS infection (75), especially with the azole antifungal agents. The concept of induction or primary therapy followed by maintenance therapy applies, as in cryptococcal meningitis (see the preceding), in chronically immunosuppressed patients. In patients with normal immune systems, careful long-term follow-up is required to identify those with relapsing infection.

As mentioned previously, amphotericin B is considered the mainstay in treatment of CNS histoplasmosis. In AIDS patients, in whom relapse is to be expected, the suggested dose is 1.0–1.5 g over 6–8 weeks, followed by maintenance therapy. Ketoconazole appears to have significant failure rates for CNS histoplasmosis, most likely attributable to low oral absorption and poor CNS penetration. Fluconazole, with its high concentrations in CSF, has been successful in at least one case of *Histoplasma* meningitis (76). Other experience with fluconazole given in doses of 100–400 mg has shown both failure and relapse in non-AIDS patients. Further studies for proper dosing for fluconazole therapy are under way. Experience with itraconazole (400 mg/day in two divided doses), on the other hand, has been encouraging for both induction and maintenance therapy and may protect against development of other serious fungal infections (77). Because of its variable absorption, serum concentrations of itraconazole should be measured (78).

Comparative trials of long-term treatment with amphotericin B and other antifungal agents will be necessary to define the best treatment and maintenance regimens in AIDS patients with *Histoplasma* meningitis. The preliminary results and favorable outcomes with itraconazole warrant further research.

Blastomyces dermatitidis

B. dermatitidis is a dimorphic fungus found in soil that predominantly causes pulmonary infection. It is endemic to the Ohio, Mississippi, and St. Lawrence River valleys but does have world-wide distribution (79,80). In the environment, it grows as a mold and reproduces by conidia borne on the end of hyphal elements called conidiophores. The conidia or spores enter the body via the respiratory tract. *B. dermatitidis* exists in tissue as a thick-walled yeast 8–15 μm in diameter. The yeast cells are multinucleate and reproduce by single buds with a broad base between parent and bud. Most cases occur in middle-aged persons, infections in men outnumber those in women, and there is no evident racial predilection.

Lung and skin are the most common sites of infection with *B. dermatitidis*. CNS infection is uncommon, manifesting as an abscess or meningitis. Meningitis is

usually a late and fulminant complication of widely disseminated blastomycosis (2). CNS involvement is reported to occur in 3–10% of cases and is usually a result of hematogenous seeding from a pulmonary source (1,81), although direct extension may occur from bony lesions in the skull or spine.

The diagnosis of CNS blastomycosis is difficult (1,81). Evaluation of CSF usually is not diagnostic. The CSF may be clear or cloudy with a pleocytosis; CSF white blood cell counts up to 15,000/mm^3 have been reported. The protein concentration is often elevated, and the glucose concentration is either normal or decreased. Less than half of the smears are diagnostic. Only 20% of patients have positive CSF cultures. Culture of ventricular fluid may be required for isolation of the fungus (1,81). The diagnosis should be strongly suspected in patients with CNS disease who have evidence of blastomycotic infection elsewhere. The diagnosis can also be made by isolating the organism from biopsy specimens. No reliable serologic test has been established. Complement-fixation, immunodiffusion, and skin tests have been useful for epidemiologic assessments but not for clinical diagnosis (80). Cross-reactivity to antigens of various fungi severely limits the specificity of these assays.

The standard treatment of individuals with CNS involvement and life-threatening blastomycosis is amphotericin B (1,81). The exact dose and duration remain unclear, but good results have been noted with a total dose of 1.5–2.5 g of amphotericin B in doses of 0.3–0.6 mg/kg daily (not exceeding 50 mg). The utility of intrathecal amphotericin has not been established, and its use is controversial. The role of the azole antifungal agents in the therapy of CNS blastomycosis has not been adequately studied.

REFERENCES

1. Treseler CB, Sugar AM. Fungal meningitis. *Infect Dis Clin North Am* 1990;4:789–808.
2. Salaki JS, Louria DB, Chmel H. Fungal and yeast infections of the central nervous system: a clinical review. *Medicine* 1984;63:108–32.
3. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. *Rev Infect Dis* 1990;12:308–29.
4. Dutcher JD. The discovery and development of amphotericin B. *Dis Chest* 1968;54:40–2.
5. Bennett JE. Antifungal agents. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*. 4th ed. New York: Churchill Livingstone, 1994:401–10.
6. Como JA, Dismukes WE. Oral azole drugs as systemic antifungal therapy. *N Engl J Med* 1994; 330:263–71.
7. Perfect JR, Durack DT. Comparison of amphotericin B and *N-d*-ornithyl amphotericin B methyl ester in experimental cryptococcal meningitis and *Candida albicans* endocarditis with pyelonephritis. *J Antimicrob Chemother* 1985;28:751–5.
8. Atkinson AJ, Bennett JE. Amphotericin B pharmacokinetics in humans. *Antimicrob Agents Chemother* 1978;13:271–6.
9. Block ER, Bennett JE, Livoti LG, Klein WI Jr, MacGregor RR, Henderson L. Flucytosine and amphotericin B: hemodialysis effects on the plasma concentration and clearance. *Ann Intern Med* 1974;80:613–7.
10. Stamm AM, Diasio RB, Dismukes WE, et al. Toxicity of amphotericin B plus flucytosine in 194 patients with cryptococcal meningitis. *Am J Med* 1987;83:236–42.
11. Diasio RB, Bennett JE, Myers CE. Mode of action of 5-fluorocytosine. *Biochem Pharmacol* 1978;27:703.
12. Bennett JE. Flucytosine. *Ann Intern Med* 1977;86:319–22.
13. Kauffman CA, Frame PT. Bone marrow toxicity associated with 5-fluorocytosine therapy. *Antimicrob Agents Chemother* 1977;11:244–7.

14. Bodey GP. Azole antifungal agents. *Clin Infect Dis* 1992;14(suppl 1):S161–9.
15. Graybill JR. Future directions of antifungal chemotherapy. *Clin Infect Dis* 1992;14(suppl 1):S170–81.
16. Baciewicz AM, Baciewicz FA Jr. Ketoconazole and fluconazole drug interactions. *Arch Intern Med* 1993;153:1970–6.
17. Grant SM, Clissold SP. Fluconazole: a review of its pharmacokinetic properties and therapeutic potential in superficial and systemic mycoses. *Drugs* 1990;39:877–916.
18. Arndt CA, Walsh TS, McCully CL, Balis FM, Pizzo PA, Poplack DG. Fluconazole penetration into cerebrospinal fluid: implications for treating fungal infections of the central nervous system. *J Infect Dis* 1988;157:178–80.
19. Dismukes WE. Azole antifungal drugs: old and new. *Ann Intern Med* 1988;109:177–9.
20. Zuckerman JM, Tunkel AR. Itraconazole: a new triazole antifungal agent. *Infect Control Hosp Epidemiol* 1994;15:397–410.
21. Perfect JR. Diagnosis and treatment of fungal meningitis. In: Scheld WM, Whitley RJ, Durack DT, eds. *Infections of the central nervous system*. New York: Raven Press, 1991:729–37.
22. Diamond RD. *Cryptococcus neoformans*. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*. 4th ed. New York: Churchill Livingstone, 1994:2331–40.
23. Levitz SM. The ecology of *Cryptococcus neoformans* and the epidemiology of cryptococcosis. *Rev Infect Dis* 1991;13:1163–9.
24. Perfect JR. Cryptococcosis. *Infect Dis Clin North Am* 1989;3:77–102.
25. Kovacs JA, Kovacs AA, Polis M, et al. Cryptococcosis in the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;103:533–8.
26. Zugar A, Louie E, Holzman RS, Simberkoff MS, Rahal JJ. Cryptococcal disease in patients with the acquired immunodeficiency syndrome. Diagnostic features and outcome of treatment. *Ann Intern Med* 1986;104:234–40.
27. Chuck SL, Sande MA. Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. *N Engl J Med* 1989;321:794–9.
28. Clark RA, Greer D, Atkinson W, Valainis GT, Hyslop N. Spectrum of *Cryptococcus neoformans* infection in 68 patients infected with human immunodeficiency virus. *Rev Infect Dis* 1990;12:768–77.
29. Diamond RD, Bennett JE. Prognostic factors in cryptococcal meningitis. A study of 111 patients. *Ann Intern Med* 1974;80:176–81.
30. Sabetta JR, Andriole VT. Cryptococcal infection of the central nervous system. *Med Clin North Am* 1985;69:333–45.
31. Zimmermann B III, Spiegel M, Laly EV. Cryptococcal meningitis in systemic lupus erythematosus. *Semin Arthritis Rheum* 1992;22:18–24.
32. Tunkel AR, Wispelwey B, Scheld WM. Pathogenesis and pathophysiology of meningitis. *Infect Dis Clin North Am* 1990;4:555–81.
33. Patterson TF, Andriole VT. Current concepts in cryptococcosis. *Eur J Clin Microbiol Infect Dis* 1989;8:457–65.
34. Johnston SRD, Corbett EL, Foster O, Ash S, Cohen J. Raised intracranial pressure and visual complications in AIDS patients with cryptococcal meningitis. *J Infect* 1992;24:185–9.
35. Perfect JR. Cryptococcal meningitis with normal cerebrospinal fluid. *J Infect Dis* 1989;160:912.
36. Goodman JS, Kaufman L, Koenig MG. Diagnosis of cryptococcal meningitis: detection of cryptococcal antigen. *N Engl J Med* 1971;285:434–6.
37. Snow RM, Dismukes WE. Cryptococcal meningitis: diagnostic value of cryptococcal antigen in cerebrospinal fluid. *Arch Intern Med* 1975;135:1155–7.
38. Boom WH, Piper DJ, Ruoff KL, Ferraro MJ. New cause for false-positive results with the cryptococcal antigen test by latex agglutination. *J Clin Microbiol* 1985;22:856–7.
39. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med* 1979;301:126–31.
40. Dismukes WE, Cloud G, Gallis HA, et al. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. *N Engl J Med* 1987;317:334–41.
41. Byrne WR, Wajszczuk CP. Cryptococcal meningitis in the acquired immunodeficiency syndrome (AIDS): successful treatment with fluconazole after failure of amphotericin B. *Ann Intern Med* 1988;108:384–5.
42. Stern JJ, Hartman BJ, Sharkey P, et al. Oral fluconazole therapy for patients with acquired immunodeficiency syndrome and cryptococcosis: experience with 22 patients. *Am J Med* 1988; 85:477–80.
43. Larsen RA, Leal M
cryptococcal men
44. Saag MS, Powder
treatment of acute
45. Bennett JE. Curre
Principles and pr
1991:3–7.
46. Larsen RA, Bozze
prostate after suc
47. Bozette SA, Lars
mans prostatic in
48. Zugar A, Schuste
cryptococcal men
1988;109:592–3.
49. Sugar AM, Saund
in patients with a
50. Bozette SA, Lars
fluconazole after
drome. *N Engl J*
51. Powderly WG, Sa
prevent relapse o
drome. *N Engl J*
52. Knoper SR, Galgi
53. Ampel NM, Wied
11:897–911.
54. Einstein HE, Johi
Infect Dis 1993;1
55. Galgiani JN. Coc
56. Stevens DA. *Coc*
practice of infecti
57. Bouza E, Dreyer
cases and review
58. Schermoly MJ, F
895–6.
59. Labadie EL, Han
theeal amphoteric
60. Galgiani JN, Cata
Intern Med 1993;
61. Tucker RM, Dent
meningitis. *Ann I*
62. Edwards JE. *Can*
of infectious dise
63. Crislip MA, Edw
64. Bayer AS, Edwar
review of the Eng
65. Lipton SA, Hicke
Am J Med 1984;7
66. Walsh TJ, Hier I
analysis of risk f
67. Smego RA, Perfe
for *Candida* men
68. Wheat LJ. Histop
69. Wheat LJ, Slama
Am J Med 1985;
70. Wheat LJ, Batter
nervous system:
71. McGinnis MR. D
72. Wheat LJ, Kohl
Histoplasma cap
73. Wheat LJ, Conn

43. Larsen RA, Leal ME, Chan LS. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS. *Ann Intern Med* 1990;113:183–7.
44. Saag MS, Powderly WG, Cloud GA, et al. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. *N Engl J Med* 1992;326:83–9.
45. Bennett JE. Current therapy of deep mycoses. In: Mandell GL, Douglas RG Jr, Bennett JE, eds. *Principles and practice of infectious diseases. Update 11*. New York: Churchill Livingstone, 1991:3–7.
46. Larsen RA, Bozzette S, McCutchan A, et al. Persistent *Cryptococcus neoformans* infection of the prostate after successful treatment of meningitis. *Ann Intern Med* 1989;111:125–8.
47. Bozette SA, Larsen RA, Chiu J, et al. Fluconazole treatment of persistent *Cryptococcus neoformans* prostatic infection in AIDS. *Ann Intern Med* 1991;115:285–6.
48. Zugar A, Schuster M, Simberkoff MS, Rahal JJ, Holzman RS. Maintenance amphotericin B for cryptococcal meningitis in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988;109:592–3.
49. Sugar AM, Saunders C. Oral fluconazole as suppressive therapy of disseminated cryptococcosis in patients with acquired immunodeficiency syndrome. *Am J Med* 1988;85:481–9.
50. Bozette SA, Larsen RA, Chiu J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. *N Engl J Med* 1991;324:580–4.
51. Powderly WG, Saag MS, Cloud G, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992;326:793–8.
52. Knoper SR, Galgiani JN. Coccidioidomycosis. *Infect Dis Clin North Am* 1988;2:861–75.
53. Ampel NM, Wieden MA, Galgiani JN. Coccidioidomycosis: clinical update. *Rev Infect Dis* 1989; 11:897–911.
54. Einstein HE, Johnson RH. Coccidioidomycosis: new aspects of epidemiology and therapy. *Clin Infect Dis* 1993;16:349–56.
55. Galgiani JN. Coccidioidomycosis. *West J Med* 1993;159:153–71.
56. Stevens DA. *Coccidioides immitis*. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*. 4th ed. New York: Churchill Livingstone, 1994:2365–75.
57. Bouza E, Dreyer JS, Hewitt WL, Meyer RD. Coccidioidal meningitis. An analysis of thirty-one cases and review of the literature. *Medicine* 1981;60:139–72.
58. Schermoly MJ, Hinthorn DR. Eosinophilia in coccidioidomycosis. *Arch Intern Med* 1988;148: 895–6.
59. Labadie EL, Hamilton RH. Survival improvement in coccidioidal meningitis by high-dose intrathecal amphotericin B. *Arch Intern Med* 1986;146:2013–8.
60. Galgiani JN, Catanzaro A, Cloud GA, et al. Fluconazole therapy for coccidioidal meningitis. *Ann Intern Med* 1993;119:28–35.
61. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med* 1990;112:108–12.
62. Edwards JE. *Candida* species. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*. 4th ed. New York: Churchill Livingstone, 1994:2289–2306.
63. Crislip MA, Edwards JE Jr. Candidiasis. *Infect Dis Clin North Am* 1989;3:103–33.
64. Bayer AS, Edwards JE Jr, Seidel JS, Guze LB. *Candida* meningitis. Report of seven cases and review of the English literature. *Medicine* 1976;55:477–86.
65. Lipton SA, Hickey WF, Morris JH, Loscalzo J. Candidal infection in the central nervous system. *Am J Med* 1984;76:101–7.
66. Walsh TJ, Hier DB, Caplan LP. Fungal infections of the central nervous system: comparative analysis of risk factors and clinical signs in 57 patients. *Neurology* 1985;35:1654–7.
67. Smego RA, Perfect JR, Durack DT. Combined therapy with amphotericin B and 5-fluorocytosine for *Candida* meningitis. *Rev Infect Dis* 1984;6:791–801.
68. Wheat LJ. Histoplasmosis. *Infect Dis Clin North Am* 1988;2:841–59.
69. Wheat LJ, Slama TG, Zeckel ML. Histoplasmosis in the acquired immune deficiency syndrome. *Am J Med* 1985;78:203–10.
70. Wheat LJ, Batterger BE, Sathapatayavongs B. *Histoplasma capsulatum* infections of the central nervous system: a clinical review. *Medicine* 1990;69:244–60.
71. McGinnis MR. Detection of fungi in cerebrospinal fluid. *Am J Med* 1983;75(1B):129–38.
72. Wheat LJ, Kohler RB, Tewari RP. Diagnosis of disseminated histoplasmosis by detection of *Histoplasma capsulatum* antigen in serum and urine. *N Engl J Med* 1986;314:83–8.
73. Wheat LJ, Connolly-Stringfield P, Kohler RB, Frame PT, Gupta MR. *Histoplasma capsulatum*

polysaccharide antigen detection in diagnosis and management of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. *Am J Med* 1989;87:396–400.
74. Wheat LJ, Kohler RB, Tewari RP, Garten ML, French MLV. Significance of *Histoplasma* antigen in the cerebrospinal fluid of patients with meningitis. *Arch Intern Med* 1989;149:302–4.
75. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immunodeficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine* 1990;69:361–73.
76. Traboschi I, Casas Parera I, Pikielny R, Scattini G, Micheli F. Chronic *Histoplasma capsulatum* infection of the central nervous system successfully treated with fluconazole. *Eur Neurol* 1992; 32:70–3.
77. Sharkey-Mathes PK, Velez J, Fetchick R, Graybill JR. Histoplasmosis in the acquired immunodeficiency syndrome (AIDS): treatment with itraconazole and fluconazole. *J Acquir Immun Defic Syndr* 1993;6:809–19.
78. Wheat LJ, Hafner R, Wulfsohn M, et al. Prevention of relapse of histoplasmosis with itraconazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1993;118:610–16.
79. Chapman SM. *Blastomyces dermatitidis*. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*. 4th ed. New York: Churchill Livingstone, 1994;2353–65.
80. Bradshear RW. Blastomycosis. *Clin Infect Dis* 1992;14(suppl 1):S82–90.
81. Gonyea EF. The spectrum of primary blastomycotic meningitis: a review of central nervous system blastomycosis. *Ann Neurol* 1978;3:26–39.

Clinical Neuropharmacol.
Vol. 18, No. 2, p. 113

The An
Invest

The American S
1980s as a group o
sion of their resear
in the ASNI is op
training faculty y
symposium, which
can Neurological A
executive committ
In 1992 I had th
"Critical Care Ne
speakers in the sym
in this new subspe
the readership of